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EXAMINER	
LEAVITT, MARIA GOMEZ	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/565,230	ERBS, PHILIPPE	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31 and 35-55* is/are pending in the application.

4a) Of the above claim(s) *1-11,30-38 and 47-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-29,39-46 and 53-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-19-2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 1-31 and 35-55 are pending. Claims 12-29 and 39-46 have been amended, claim 32-34 have been cancelled and claims 53-55 have been added by Applicants' amendment filed on 12-05-2008. Claims 1-11, 30, 31, 35-38 and 47-52 were previously withdrawn from consideration as being directed to non-elected inventions pursuant to 37 CFR1.14(b), there being no allowable generic or linking claim. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.
3. Therefore, claims 12-29, 39-46 and 53-55 are currently under examination to which the following grounds of rejection are applicable.

Withdrawn Rejections/objection in response to Applicants' arguments or amendments:

Drawings objection

In view of Applicants' submission of a corrected drawing sheet for Figure 1, objection to the drawings has been withdrawn.

Objection Specification

In view of Applicants'' submission of a substitute specification, objection to the specification has been withdrawn.

35 USC 101-non-statutory subject matter

In view of Applicants' amendment of claim 12-29 and 39-46 to recite "isolated" and thus indicate the hand of the inventor, rejection of claims 12-29 and 39-46 under 35 USC 101-non-statutory subject matter, has been withdrawn.

Claim Rejections - 35 USC § 112- Second Paragraph

In view of Applicants amendment of claims 16 and 17 to delete the recitation of "derived", rejection of claims 16 and 17 under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language has been withdrawn.

Claim Rejections - 35 USC § 112- First paragraph- Lack of Enablement

In view of Applicants' amendment of claim 12 to recite " an isolated nucleotide sequence encoding SEQ ID NO:2 fused in frame with a second polypeptide having cytosine deaminase activity" , and further in view of Applicants remarks, in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art at the time of filing the present application and further in view of reconsideration of search under different premises, rejection of claims 12-29 and 39-46 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been withdrawn.

In view of the withdrawn rejection, applicant's arguments are rendered moot.

New grounds of rejection

Claim Rejections - 35 USC § 103(a)

To the extent that the instant claims are drawn to an isolated nucleotide sequence encoding the polypeptide of SEQ ID NO:2 fused in frame with a second polypeptide having cytosine deaminase activity, the following rejection applies.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 12-17, 20, 22-29, 39-46 and 54-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erbs et al (WO99/54481, Date of Publication Oct. 28, 1999; see SCORE Search Results Details for Application 10565230 and Search Result us-10-565-230-2.rag, Result **No. 2**) in view of Kern et al.(Gene, 1990, pp. 149-157, **see** SCORE Search Results Details for Application 10565230 and Search Result us-10-565-230-2.p2n.rge. Result **No. 4**). Citations are from the National Stage U.S. Patent No. 6,596,533. The National Stage is deemed an English language translation of the PCT). **This is a new rejection necessitated by amendment of the claims in the response filed 12/05/2008.**

Erbs et al., discloses an isolated nucleotide sequence encoding a mutant uracil phosphoribosyl CC transferase (UPRTase) protein and related fusion protein having 99.6% homology to the claimed polypeptide of SEQ ID NO.2 (SEQ ID NO: 2 is a 216 aa residue polypeptide) (see Search Result us-10-565-230-2.rag, Result No. 2). The only difference between the protein of Erbs et al., and the instantly claimed protein of SEQ ID NO:2 is the substitution of an **Arg** by a **Ser** at position 26 of SEQ ID NO: 2 (see Search Result us-10-565-230-2.rag, Alignment Result No. 2). Moreover, Erbs et al., teaches that a mutated FUR1 gene which encodes a UPRTase, deleted in its N-terminal part, is used to generate fusion protein which is produced by the hybrid FCY1::FU1.DELTA.105 gene which results from the in-frame fusion of the FCY1 and truncated FUR1 genes (col. 3, lines 3-9; lines 30-41) **Current claim 12**. Moreover, Erbs discloses the UPRTase protein, or its fusion proteins (particularly with CDase), nucleic acids encoding them and derived recombinant vectors, virus particles and transformed cells are useful in human and veterinary medicine, for gene therapy or production of recombinant proteins (col. 3, lines 30-41; col. 6, lines 55-65; col. 11,lines 22-30) **(Current claims 40, 42 and 44)**. Viral vectors include vaccinia virus, in particular MVA, canarypoxvirus, and others (col. 7, lines 18-26). **(Current claims 14, 16, 17 and 55).** Erbs teaches that the transfectional efficiency and/or stability of the vector can be improved by cationic lipids (col. 6, line 50) **(Current claims 15 and 54)**. Expression of the FUR1deleted 105 is under the control of the early CMV promoter or other promoters (col. 16, line 34; col. 23, lines 25-35; col. 8, lines 30-62) **(Current claims 13, 20 and 24)**. Isolated vector with deleted regions which are essential for replication are disclosed throughout the whole document, for example at col. 7, lines 50-56; col. 24, lines col. 23, lines 15-23) (Current **claims 22 and 23**). In addition, Examples 7 discloses the combination of the

FCU1 suicide gene and genes encoding cytokines including IFN-γ and IL-2 (col. 10, lines 49-52; col. 24, line 16) **(Current claim 25, 26 and 43)**. Furthermore, Erbs et al., discloses methods for preparing viral particles wherein the defective essential functions are completed in trans by means of a complementing cell line (col. 9, lines 47-56; col. 7, lines 55-60; col. 10, lines 34-38;col. 11, lines 10-15; 9) ; **(Current claims 27, 28, 29, 39, 41, 45 and 46)**. Moreover, Erbs et al., discloses that the fusion polypeptide may be a deletion mutant of a native UPRTase. The deletion is preferably located in the N-terminal region of the original UPRTase including deletions affecting one or more residues which may or may not be continuous in the primary structure (col. 4, lines 10-25).

Erbs et al., et al., does not particularly teach a polypeptide sequence having 100% homology to SEQ ID NO:2.

However, at the time the invention was made, the nucleotide sequence of the yeast FURI gene and deduced aa for UPRTase were commonly used sequences known in the art as evidenced by Kern et al.,. Indeed, Kern et al discloses a 753 bp open reading frame encoding a UPRTase protein of 251 aa. The native UPRTase protein contains 2 Met residues, one at position 1 and the second at position 36. Moreover, Kern discloses single bp changes located in different regions of the gene leading to the lost of UPRTase activity, including a *fur1 -8* allele wherein an Arg^{61} residue is changed into Ser (p. 155, col. 2, paragraph 1). It is noted that this Arg residue corresponds to the aa at position 26 in SEQ ID NO:2 (see SCORE Search Results Details for us-10-565-230-2.p2n.rge. Result **No. 4).**

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art to modify the isolated mutated FUR1 gene encoding the polypeptide of SEQ ID NO:2 in the

fusion protein which encodes a two-domain enzyme possessing CDase and UPRTase activities as taught by Erbs, with a mutated FUR1 gene that comprises a change of Arg to Ser as taught by Kern, particularly because Kern discloses by replacing the Arg residue at position 61 for a Ser abrogates UPRTase activity. Moreover, the state of the art teaches that it is well established in the art to make and test oligos of different sizes in the design of drugs to interfere with gene expression of a known sequence. The manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. As all the elements where known in the prior art, one of ordinary skill in the art would have had a reasonable expectation of success in making an isolated mutant nucleotide sequence as claimed by combining the disclosure of Erbs teaching an isolated mutant nucleotide sequence encoding the mutated polypeptide of SEQ ID No. 2 fused in frame with a second polypeptide possessing CDase activities and Kern actually exemplifying a mutated FUR1 gene encoding a UPRTase with single point mutations in its N-terminal part the including changing the Arg residue at position 61 for a Ser.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Erbs et al (WO99/54481, Date of Publication Oct. 28, 1999; see SCORE Search Results Details for Application 10565230 and Search Result us-10-565-230-2.rag, Result **No. 2**) in view of Kern et al.(Gene, 1990, pp. 149-157, **see** SCORE Search Results Details for Application 10565230 and Search Result us-10-565-230-2.p2n.rge. Result **No. 4**) as applied to claim 12-17, 20, 22-29, 39-46 and 54-55 above, and further in view of Faure et al., (Date of publication, 1986, EP 0206920;

An official translation of the document has been requested). **This is a new rejection necessitated by amendment of the claims in the response filed 12/05/2008.**

The teachings of Erbs and Kern are outlined in the paragraphs above.

The combined disclosure of Erbs and Kern fails to teach a promoter of the thymidine kinase (TK) that is 7.5K gene.

However, at the time the invention was made, Faure et al., exemplifies cloning and expression of the IFN-γ under the control of the TK of 7.5K (page 3, lines 10-15; page 4, line 20-25).

Therefore, it would have been obvious for one of ordinary skill in the art to have employed any of the known viral vector promoters for sufficient expression of a gene of interest including a TK of 7.5K, as exemplified by Faure et al., in the viral vector taught by Erbs and Kern in order to target expression of a gene of interest in a cell with a reasonable expectation of success, particularly since Faure evidences successfully expression of IFN-γ in Vero cells by using a viral vector operably linked to the TK of 7.5K. Thus, one of ordinary skill in the art would have been motivated to have employed any of the known specific promoters, including TK of 7.5K, as exemplified by Faure, in the viral vector taught by Erbs and Kern in order to express a gene of interest in a cell.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Erbs et al (WO99/54481, Date of Publication Oct. 28, 1999; see SCORE Search Results Details for Application 10565230 and Search Result us-10-565-230-2.rag, Result **No. 2)**, in view of Kern et al.(Gene, 1990, pp. 149-157, **see** SCORE Search Results Details for Application 10565230 and

Search Result us-10-565-230-2.p2n.rge. Result **No. 4**) as applied to claim 12-17, 20, 22-29, 39-46 and 54-55 above and further in view of Sutter et al., (FEBS Letters, 1995, pp 9-12) and Carroll (Vaccine 1997, pp. 387-394). **This is a new rejection necessitated by amendment of the claims in the response filed 12/05/2008.**

The teachings of Erbs and Kern are outlined in the paragraphs above.

The combined disclosure of Erbs and Kern fails to teach the MVA genome with deletions of I, II, III, IV and IV .

However, at the time the invention was made, the complete genome DNA sequence of the highly attenuated MVA was well known in the art as evidenced by Sutter et al., including precise restriction maps and naturally occurring deletion II, See page 10, Fig, 1. Schematic representation of map of the genome of MVA. Likewise, Carroll evidences the use of MVA as an effective recombinant vector for expression of heterologous genes in mammalian cells, particularly vectors with the deleted region III of MVA (p. 387, col. 2, paragraph 2). Furthermore, Carroll discusses the use of recombinant MVA an immunogen in cancer immunotherapy, in part, because of its safety (p. 391, col. 1 and 2) .

Therefore, in view of the benefits of using a modified MVA as a safe vector for the development of recombinant cancer vaccines as taught by Sutter and Carroll, it would have been obvious for one of ordinary skill in the art to have modify the viral vector disclosed by Erbs and Kern with a modified MVA comprising a deletion of the II or III region for use as a safe vector in anti-cancer vaccines. The claims would have been obvious because a person of ordinary skill has a good reason to pursue the known options in his grasp. In turn, because an isolated recombinant modified MVA has the proprieties predicted by the prior art it would have been

obvious to make the modified MVA with insertion of a nucleotide sequence at known naturally occurring deletions of its genome.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-29, 39-46 and 53-55 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by amendment of the claims in the response filed 12/05/2008.**

Claim 12 recites "an isolated nucleotide sequence encoding SEQ ID NO:2". It is well established in the art that a nucleotide sequence encodes a polypeptide or a protein. Thus it is unclear how the product encodes by an isolated nucleic acid encodes is identified by recitation of a sequence number. In addition, claim 12 recites "a second polypeptide". However, claim 12 does not require "a the first polypeptide". Thus it is unclear in reference to what the the second polypeptide is made. Thus, the metes and bounds of the claim as whole are unclear.

Claim 53 is indefinite in the reciting "The polypeptide of claim 12, wherein the fusion protein is SEQ ID NO: 1". There is no antecedent basis for "the polypeptide" in claim 12 as claim 12 recites "a second polypeptide". Moreover, there is not an antecedent base for "the fusion protein" in claim 1 from which it depends. Thus, the metes and bounds of claim 53 as whole are unclear.

Claims 13-29, 39-46 and 53-55 are indefinite insofar as they depend from claim 38.

Conclusion

Claims 12-29, 39-46 and 53-55 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633